Unlocking New Therapeutic Possibilities

Oral selective STAT3 inhibitors demonstrate differentiated efficacy and safety potential in preclinical models of Th17 mediated skin inflammation

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No Disclosures

Dr. Seong Kim
STAT3 Inhibition Has Potential Clinical Applications Across Multiple Inflammatory and Autoimmune Diseases

Small molecule STAT3 inhibitors may provide an oral alternative to clinically validated biologics.
Src Homology 2 (SH2) domains are highly conserved protein domains that have long been recognized as attractive drug targets

- Small protein modules made up of ~100 amino acids
- 120 human SH2 domains
- The SH2 domain of STAT proteins is required for:
  - Binding to cytokine receptors via the SH2 domain and phospho-tyrosine motifs on the receptor
  - Dimerization of STAT proteins occurs by reciprocal interactions with each monomer's SH2 domain; STAT DNA binding and transcriptional activity requires dimerization

Recludix has created a platform of integrated technologies enabling SH2 domain inhibitor discovery
<table>
<thead>
<tr>
<th></th>
<th>REX-5376</th>
<th>REX-7117</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biochemical Potency</strong></td>
<td>0.15 nM</td>
<td>0.15 nM</td>
</tr>
<tr>
<td>(SH2scan $K_D$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cellular Potency</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>($p$STAT3 $IC_{50}$ in human PBMCs, 20hrs)</td>
<td>0.7 nM</td>
<td>1.1 nM</td>
</tr>
<tr>
<td><strong>Cellular Selectivity (PBMCs)</strong></td>
<td>~1-2X vs. STAT1</td>
<td>~20X vs. STAT1</td>
</tr>
<tr>
<td></td>
<td>&gt;150X vs. STAT2/4</td>
<td>&gt;20-30X vs. STAT2</td>
</tr>
<tr>
<td></td>
<td>&gt;1,000X vs. STAT5/6</td>
<td>&gt;1,000X vs. STAT4/5/6</td>
</tr>
</tbody>
</table>

**SH2 Family Selectivity**

STAT3 potency and selectivity maintained across biochemical and cellular assays
Primary human T cells cultured under Thelper (Th) skewing conditions in the presence of compounds.

<table>
<thead>
<tr>
<th>T Cell function</th>
<th>General Adaptive Immune response</th>
<th>Defense against viruses and bacteria</th>
<th>Defense against extracellular pathogens</th>
<th>Defense against parasites and mediation of antibody responses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T Cell Activation (CD25 IC₅₀)</td>
<td>Th1 Cell Function (IFNγ IC₅₀)</td>
<td>Th17 Cell Function (IL-17A IC₅₀)</td>
<td>Th2 Cell Function (IL-5 IC₅₀)</td>
</tr>
<tr>
<td>REX-7117</td>
<td>&gt;10,000 nM</td>
<td>&gt;3,000 nM</td>
<td>14 nM</td>
<td>&gt;3,000 nM</td>
</tr>
<tr>
<td>REX-5376</td>
<td>&gt;10,000 nM</td>
<td>&gt;2,000 nM</td>
<td>11 nM</td>
<td>&gt;3,000 nM</td>
</tr>
<tr>
<td>TYK2 Inhibitors</td>
<td>Deucravacitinib</td>
<td>&gt;3,000 nM</td>
<td>260 nM</td>
<td>~3,300 nM</td>
</tr>
<tr>
<td></td>
<td>TAK-279</td>
<td>&gt;10,000 nM</td>
<td>69 nM</td>
<td>&gt;3,000 nM</td>
</tr>
<tr>
<td>JAK Inhibitors</td>
<td>Tofacitinib</td>
<td>340 nM</td>
<td>74 nM</td>
<td>20 nM</td>
</tr>
<tr>
<td></td>
<td>Upadacitinib</td>
<td>39 nM</td>
<td>36 nM</td>
<td>4 nM</td>
</tr>
<tr>
<td></td>
<td>Baricitinib</td>
<td>110 nM</td>
<td>210 nM</td>
<td>15 nM</td>
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Selectivity relative to Th17 inhibition: □ □ □ □ □ □ □ □ □ □ □ □ □ □ □

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Targeting STAT3 uniquely spares the broader T cell compartment.
Oral STAT3 Compounds in Dogs Achieve In Vivo Selective and Sustained Target Inhibition

Dog PBMCs evaluated for STAT inhibition following single day oral dosing

**REX-5376**
(30 mg/kg, PO)

**REX-7117**
(30 mg/kg, PO)

**Baricitinib**
(0.1 mg/kg, PO - clinically relevant dose)

**Deucravacitinib**
(0.3 mg/kg PO - clinically relevant dose)

Recludix Pharma - SID 2024

Recludix Pharma internal data
REX-7117 Demonstrates Efficacy After Oral Dosing in a Murine IL-23-Induced Th17 Model of Psoriasis

- Preclinical model used in the development of anti-IL-17 and anti-IL-23 biologics therapies
- REX-7117 dose was selected to match PD profile to that observed in dog at 15 mg/kg QD
- Deucravacitinib clinically relevant dose determined from regulatory filings and publications

**Mouse pSTAT3 Inhibition**

**IL-23 Induced Psoriasis Model**

REX-7117 efficacy comparable to anti-IL-17A biologic and improved relative to deucravacitinib
Selective STAT3 inhibitors have potential JAK/TYK2 safety differentiation advantages
Selectively Targeting STAT3 Does Not Impair Interferon-Mediated Inhibition of VZV Viral Replication

Human retinal epithelial cells preincubated with STAT3 or JAK/TYK2 inhibitors then either IFNβ or IFNγ cytokines, followed by VZV infection. Measurement of viral IE62 and ORF63 protein expression 48hrs post-infection.

STAT3 inhibition spares IFN dependent anti-viral immunity and differentiates from JAK/TYK2 therapies.
STAT3 Inhibition Selectively Targets Key Inflammatory Cytokines and Downstream Th17 Cell Pathogenesis

Pro-inflammatory cytokines
- Guselkumab
- Tildrakizumab
- Risankizumab
- Vixarelizumab
- Tocilizumab
- Nemolizumab
- Fezakinumab
- LEO138959

Anti-Viral Immunity
- IFNα
- IFNβ
- IFNω
- IFNκ
- IFNγ

Opportunistic Infections
- anti-viral
- innate immunity

Hematologic Homeostasis
- Red Blood Cells
- Platelets
- Neutrophils
- Monocytes

Clinical Efficacy
- Selective STAT3 inhibitors have potential JAK/TYK2 safety differentiation advantages

Opportunistic Infections
- Anemia, Thrombocytopenia, Neutropenia

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## Hematology Homeostasis

**Erythropoiesis**
- Erythropoietin (EPO) or Thrombopoietin (TPO) mediated pSTAT5 signaling in reporter cell lines

**Thrombopoiesis**

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<th>STAT3 Inhibitors</th>
<th>IL-6-Driven pSTAT3 Activation in PBMCs (IC&lt;sub&gt;50&lt;/sub&gt;)</th>
<th>EPO-Induced STAT5-Driven Transcription (IC&lt;sub&gt;50&lt;/sub&gt;)</th>
<th>TPO-Induced STAT5-Driven Transcription (IC&lt;sub&gt;50&lt;/sub&gt;)</th>
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<td>1 nM</td>
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<td>55 nM</td>
<td>46 nM</td>
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Selectivity relative to PBMC pSTAT3 inhibition:
- **>30X**
- **10-30X**
- **<10X**

**JAK inhibitors impair hematopoietic signaling at equivalent concentrations to their anti-inflammatory mechanism of action**
Recludix has generated orally available, potent and selective small molecule STAT3 inhibitors active against Th17 driven inflammation.

Selective STAT3 targeting has the potential for both enhanced efficacy and safety relative to JAK/TYK2 family inhibitors.

STAT3 inhibition has potential clinical applications across Th17 driven diseases, including Psoriasis, Psoriatic Arthritis, Rheumatoid Arthritis, and Inflammatory Bowel Disease.

Recludix has created a discovery platform integrating multiple technologies facilitates drugging of previously ‘undruggable’ targets, including other STAT family members.

Please visit poster #738 in Poster Session 2.
Thank you

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bd@recludix.com

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